REMARKS

Claims 9-23 were pending. Claims 15, 20 and 22 are amended herein. New claim 24 is added. Support for the new claim is found in the specification at, *inter alia*, page 4, lines 10-18. It is believed that no new matter has been added. Claims 9-24 are pending. No claim is allowed.

Rejections Under 35 U.S.C. § 101 and § 112, first paragraph

Claims 9-23 are rejected under 35 U.S.C. § 101 for reasons already of record. In brief, the Examiner asserts that the claimed invention lacks a well established utility because the specification does not teach which specific signal transduction pathway that CD200R is involved in any specific cell type that leads to a specific disease. According to the Examiner, there is no teaching whether the involvement of macrophages and dendritic cells in the disclosed diseases such as multiple sclerosis result from the expression of CD200 antigen. The Examiner also argues that the acceleration of EAE onset in a murine model following administration of a human IgG OX2RH1 fusion protein indicates that the claimed antibody cannot be used to treat disease. Applicants traverse this rejection for reasons already of record as well as those discussed below.

In rejecting the presently claimed antibodies and fragments thereof, the Office has apparently taken the position that only certain evidence substantiated by actual experimental data establishes a patentable utility. However, such is not the legal standard for the utility requirement. A disclosed utility for the claimed subject matter satisfies the utility requirement under § 101 absent evidence which would cast doubt on the objective truth of the disclosed utility. *Manual of Patent Examination Procedure* (hereinafter "MPEP") § 2107.02 (III)(A) (8th ed., Rev. 4, 2006). There is no legal requirement that the disclosed utility must be supported by conclusive experimental data. According to the MPEP,

> [a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Id. at page 2100-39 (emphasis original)(citations omitted). An applicant is only required to provide evidence that, when considered as a whole, leads the skilled artisan to conclude that the asserted utility is more likely than not true. *See* MPEP § 2107.03 (II).

Applicants respectfully submit that the Office has adopted an incorrect standard in maintaining the instant rejection. Specifically, the Office is requiring that a certain and exact disclosure of the biological role of the CD200R protein and its significance in a particular disease must be described if the specification is to fulfill the utility requirement of §§ 101 and 112. In essence, the Office is requiring proof beyond a reasonable doubt regarding the precise mechanism of action of the CD200R protein in a specific cell and/or a particular disease. However, such is not and has never been the correct legal standard for utility.

While only one well-established utility is required, the instant specification discloses more than one specific, substantial and credible utility that satisfies the requirements of §§ 101 and 112. The specification expressly discloses that antibodies that bind CD200R have significant therapeutic value in the treatment of diseases or conditions where modulation of function of myeloid lineage cells is desirable. *See* the specification at page 74, lines 28-35. According to the specification, such diseases and conditions include

> autoimmunity; an inflammatory condition; tissue specific autoimmunity; degenerative autoimmunity; rheumatoid arthritis; atherosclerosis; multiple sclerosis; vasculitides; delayed hypersensitivities; skin grafting; a transplant; spinal injury; stroke; neurodegeneration; or ischemia.

See the specification at page 75, lines 22-26. The specification further states that:

> [in] cases where leukocytes, including macrophage/myeloid lineage cells, expressing the OX2R [CD200R] are involved in pathologies and contribute to disease process, it may be desirable to inhibit the function of these cells. This may be achieved by appropriate stimulation of an OX2R [CD200R], such that the cell-inhibitory activities of receptor signaling are mobilized.

See the specification at page 75, lines 7-12. In other words, the specification discloses modulation of CD200R activity, particularly its inhibitory activity, in a specific population of cells, *i.e.*, those of myeloid lineage, in a specific group of diseases by antibodies specific for CD200R is useful in treatment of certain diseases. Such a utility is substantial, having a real world use in modulating the disclosed diseases and conditions using antibodies specific for CD200R. The disclosed utility also

is credible to a person of skill in the art as the expression pattern of CD200R in the disclosed cell types in combination with the known function of these cells in disease are sufficient evidence that render the asserted utilities more likely than not true.

Moreover, objective evidence of record overwhelmingly substantiates the asserted utilities as accurate. Briefly, mice lacking the ligand for CD200R, *i.e.*, CD200 -/- mice, have increased numbers of activated macrophages and a profound increase in susceptibility to autoimmune diseases affecting the brain and joint. *See* Hoek et al., *Science* 290:1768 (2000) (already of record). This increased susceptibility to autoimmune disease implicated the CD200R as a regulator of autoimmunity. Subsequent studies demonstrated that CD200R modulators do in fact inhibit autoimmune disease and transplant rejection in art-recognized animal models. *See* Gorczynki et al., *Clin. Immunol.* 104:256-64 (2002) (demonstrating CD200Fc as inhibitor in murine rheumatoid arthritis model) (already of record); Gorczynki et al., *Eur. J. Immunol.* 31:2331-7 (2001) (demonstrating that anti-CD200R antibody elicited immunosuppression and thereby inhibited allograft rejection) (already of record); and WO 03/077947 (demonstrating anti-CD200R antibodies act as inhibitors in murine rheumatoid arthritis model) (already of record). Signaling through the human CD200R downregulated macrophage (cells of the myeloid lineage) activation in the manner predicted by the multitude of murine and rat studies involving CD200/CD200R interactions, supporting a role for CD200R in the inhibition of macrophage activity. *See* Foster-Cuevas et al., *J. Virol.* 78:7667-76 (2004) (already of record). Antibodies specific for human CD200R inhibited degranulation of human mast cells, a primary sentinel of peripheral tissue inflammatory immune responses implicated in a number of autoimmune diseases including multiple sclerosis and arthritis. *See* Cherwinski et al., *J. Immunol.* 174:1348-56 (2005) (already of record). Collectively, these references demonstrate that CD200R can act as an inhibitory signal in macrophages and mast cells, both of the myeloid lineage, and inhibits pathology in art-recognized models of autoimmune disease, rheumatoid arthritis, and transplantation rejection, confirming the accuracy of the asserted utilities. Taken together with the disclosure in the specification, Applicants easily meet the utility requirement under 35 U.S.C. § 101.

Applicants respectfully disagree with the Examiner's interpretation of the Wright reference (already of record) as support for the assertion that "said antibody cannot be used to treat disease".

See Action dated July 13, 2006 at page 4. Wright discloses a CD200R antibody that acts to block the interaction between CD200R and its ligand. In other words, this antibody is antagonistic for the function of CD200R. As disclosed in detail above, CD200R typically delivers an inhibitory signal when binding its ligand. Thus, an antibody that elicits a signal like the ligand delivers an inhibitory signal, *i.e.*, an agonist antibody. The absence of such an inhibitory signal should and does exacerbate disease, the result disclosed by Wright. On the other hand, an agonist antibody such as those disclosed in Gorczynki, WO 03/077947, Foster-Cuevas, and Cherwinski successfully modulate disease as disclosed in the specification. In sum, Wright is not contrary to the disclosed utilities of CD200R, but when properly understood, provides additional support for those utilities.

Finally, Applicants respectfully submit that the law does *not* require the certain and exact data on biological role or function demanded by the Examiner. The Board of Patent Appeals and Interference ("the Board") recently acknowledged the absence of such a requirement in *Ex parte* Hedrick. *See* Exhibit A. In *Ex parte* Hedrick, the Board considered an application claiming a compound that bound a novel cytokine (*e.g.*, an antibody). The specification disclosed that the cytokine played a role in inflammation based (at least in part) on structural and sequence similarities between the cytokine and the IL-1 family of cytokines. The claims were rejected under 35 U.S.C. § 101. Applicants provided post-filing evidence that the novel cytokine played a role in psoriasis, an inflammatory condition of the skin. The Examiner maintained the rejection, alleging that disclosure that the cytokine played a role in inflammation was insufficient as (1) many compounds play a role in inflammation, (2) psoriasis was not specifically disclosed as an inflammatory condition where the cytokine acted, and (3) the precise function of the cytokine in psoriasis was not disclosed.

Upon Appeal, the Board reversed the examiner's utility rejection and held that the specification satisfied the utility requirement. According to the Board,

> [once] it is accepted that the [cytokine] either contributed to or inhibits the inflammatory response, it seems likely that those skilled in the art would recognize the claimed binding compounds are useful for either inhibiting or promoting inflammation. The examiner has not argued that compounds that promote inflammation lack utility, or that compounds that inhibit inflammation lack utility. Since the examiner apparently accepts the claimed compounds will have one of these

> two activities, the disclosure that IL-1δ has a role in inflammation seems adequate to support utility.

See Exhibit C at page 10. Moreover, the Board held that the post-filing evidence was acceptable because it was used to show the accuracy of the utility disclosed in the specification. *See id.* at pages 10-11. The Board then noted that pharmaceutical inventions *necessarily* include the expectation of further research and development. *See id.* at page 11.

The facts in the instant application are very similar to those of the Board decision discussed in *Ex parte* Hedrick. The specification discloses a discrete expression pattern of CD200R in myeloid cells (including macrophages and mast cells) and identifies structural motifs in CD200R known to participate in cellular signaling. The specification discloses a role for CD200R in the regulation of myeloid cells, particularly providing inhibitory signal in diseases and conditions such as autoimmune disease, rheumatoid arthritis, multiple sclerosis, and transplant rejection. Objective evidence demonstrates that CD200R mediates an inhibitory signal in macrophages and mast cells and agonist antibodies successfully modulate murine models of rheumatoid arthritis and transplantation rejection as expressly disclosed in the specification. Nothing more is required to meet the utility requirement.

As the specification provides adequate utility for the reasons discussed above, Applicants submit that the specification also provides sufficient written description on how to make and use the claimed antibodies and fragments thereof.

For at least these reasons, Applicants respectfully submit that the rejection under 35 U.S.C. §§ 101 and 112, first paragraph are overcome and should be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 9-23 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. According to the Examiner, the specification fails to teach or provide any working example that any therapeutic effect is seen in patients or animal model when the antibody is administered. Applicants traverse this rejection.

Applicants respectfully submit that the specification as filed provides reasonable enablement for the claimed antibodies and fragments thereof. The specification provides guidance regarding a

specific sequence for the protein that is bound by the claimed antibodies and fragment thereof, methods of making the protein (page 57, line 29 to page 64, line 33), methods of making antibodies (page 57, line 35 to page 70, line 12), as well as guidance regarding kits containing the claimed antibody or fragment thereof (page 70, line 14 page 74, line 25). The specification also provides guidance for the therapeutic use of antibodies at page 74, line 27 to page 79, line 7. Thus, a person of skill in are would be able to make and use the claimed antibodies and fragments thereof. Applicants note that the claim is not directed to a method of treatment or the treatment of multiple sclerosis *per se*. Therefore, there is no basis for evaluating the claims for enablement based on such methods when the claims are drawn to compounds (*i.e.*, binding antibodies or fragments thereof). At the very least, the specification enables the use of such antibodies in a diagnostic kit. *See, e.g.*, the specification at page 71, line 21 to page 74, line 25. As this use reasonably correlates with the scope of the claimed antibodies and fragments thereof, the specification provides reasonable enablement for the claims. *See* MPEP § 2164.01(c) ("if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention").

In view of the above, Applicants respectfully request the rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 15, 20 and 22 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in the recitation of the limitation "or a fragment thereof".

Claims 15, 20 and 22 are amended herein to remove the limitation "or a fragment thereof", rendering the rejection moot.

Accordingly, it is believed this basis for rejection may be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 140942000900.

Respectfully submitted,

Dated: November 6, 2006

By: _____

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